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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/037,472	03/10/98	DUFF G	33174.5

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EXAMINER	
MYERS,C	
ART UNIT	**PAPER NUMBER**
1655	12

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/037,472	Duff
Examiner	**Group Art Unit**
Carla Myers	1655

☒ Responsive to communication(s) filed on *Sep 21, 1998*

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *one* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *1-9* is/are pending in the applicat

Of the above, claim(s) _____ is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-9* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *3*

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

1. Applicants intent to claim priority to GB 9621129.7 is acknowledged. However, Applicant has not complied with the requirements of 37 CFR 1.63(c), since the oath or declaration does not acknowledge the filing of any foreign application. A new oath or declaration is required in the body of which the present application should be identified by application number and filing date.

Furthermore, the first line of the specification must be amended to clarify the relationship between the instant application and PCT/GB97/02790 because the statement that the instant application "is based on copending PCT Patent Application GB97/02790" is confusing and unclear. The specification should be amended to indicate that this application is the national phase of PCT/GB97/02790 or to indicate that the instant application is a continuation of PCT/GB97/02790, as appropriate.

2. It is noted that reference "AG" in the Information Disclosure Statement filed September 21, 1998 has been considered but has been lined through because this citation does not include a date of publication or a source. Furthermore, document "B1" has also been considered but has been lined through because it is not proper to cite a "search report" in an IDS.

3. The disclosure is objected to because of the following informalities: .

On page 24 of the specification, the sentence "[There was text missing here in the original UK filing]" should be deleted.

4. Claims 7 and 8 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim does not properly depend from another multiple depend claim. See MPEP § 608.01(n).

5. Claims 4-9 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods for predicting a predisposition to clinically significant macular edema by detecting the presence of a genotype selected from the group consisting of (a) IL-1A (-889) 2,2 and ILb (-511) 2,2; (b) IL-1A (-889) 1,2 and ILb (-511) 2,2; and (c) IL-1A (-889) 2,2 and ILb (-511) 1,2, and methods for predicting a patient's predisposition to proliferative diabetic retinopathy wherein the presence of IL-1RN (VNTR) 2,2 is indicative of a decreased likelihood that the patient is predisposed to proliferative diabetic retinopathy, does not reasonably provide enablement for methods which detect the presence of IL-1 RN (VNTR) alleles as indicative of any disease other than proliferative diabetic retinopathy, methods which detect the presence of the 1L-1A and ILb alleles as indicative of any disease other than clinically-significant macular edema, methods which detect polymorphisms other than IL-1A (-889), or ILb (-511) or IL-1RN (VNTR) or methods which identify polymorphism patterns in "other genes associated with sight-threatening diabetic retinopathy". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The specification has identified three alleles in the IL-1 gene cluster that are useful for predicting a patients increased susceptibility to different forms of sight-threatening diabetic

retinopathy. In particular, the specification teaches that the presence of IL-1 RN (VNTR) allele 2, 2 provides a protective effect against the development of proliferative diabetic retinopathy (see page 15 of the specification). No protective effect was found in patients which possess only one IL-1RN (VNTR) allele 2. The specification (page 16) also teaches that there is an increase risk of developing clinically-significant macular edema in diabetic patient's possessing one of the following genotypes: (a) IL-1A (-889) 2,2 and ILb (-511) 2,2; (b) IL-1A (-889) 1,2 and ILb (-511) 2,2; or (c) IL-1A (-889) 2,2 and ILb (-511) 1,2. Accordingly, the specification has enabled methods for predicting a patient's predisposition to proliferative diabetic retinopathy wherein the presence of IL-1RN (VNTR) 2,2 is indicative of a decreased likelihood that the patient is predisposed to proliferative diabetic retinopathy and methods for predicting a predisposition to clinically significant macular edema by detecting the presence of a genotype selected from the group consisting of (a) IL-1A (-889) 2,2 and ILb (-511) 2,2; (b) IL-1A (-889) 1,2 and ILb (-511) 2,2; and (c) IL-1A (-889) 2,2 and ILb (-511) 1,2.

The specification is not enabling for methods which detect alleles other than the ILb (-511) allele 2, IL-1A (-889) allele 2 or IL-1RN (VNTR) allele 2 polymorphisms because the specification has not taught any additional alleles that are associated with different forms of sight-threatening diabetic retinopathy and it is highly unpredictable as to what other alleles in the IL-1 gene cluster or what other genes in general contain alleles associated with sight-threatening diabetic retinopathy. There is no universal association between the presence of alleles in the IL-1 gene cluster and the occurrence of sight-threatening diabetic retinopathy. The art has not established a

correlation between any alleles of IL-1 and the occurrence of disease which would allow for a general relationship to be established between the presence of an IL-1 gene cluster allele and sight-threatening diabetic retinopathy. The specification has not taught any particular attribute of the IL-1 RN (VNTR) allele 2, or ILb (-511) allele 2 or IL-1A (-889) allele 2 that could be extrapolated to other alleles in order to predictably identify other alleles in these genes and other IL-1 genes or any other unstated gene which would be predictive of sight-threatening diabetic retinopathy. Accordingly, there is no predictable means for determining which of the multitude of known and unknown alleles of IL-1 genes and other genes would be associated with sight-threatening diabetic retinopathy. Additional polymorphisms could only be identified by one of skill in the art through extensive trial and error experimentation. In addition, with respect to claim 9, the specification has not identified a single non-interleukin gene which is associated with sight-threatening diabetic retinopathy and has not provided sufficient guidance to enable one of skill in the art to predictably identify "DNA genetic polymorphism patterns for other genes associated with sight-threatening diabetic retinopathy". Case law has established that "(t)o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *In re Wright* 990 F.2d 1557, 1561. *In re Fisher,* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) it was determined that "(t)he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art". Furthermore, the Court in *Genetech Inc. v Novo Nordisk* 42 USPQ2d 1001 held that "(I)t is the specification, not the knowledge of one

skilled in the art that must supply the novel aspects of the invention in order to constitute adequate enablement". In the instant case, the specification has identified only the IL-RN (VNTR) 2,2 allele as being correlated with proliferative diabetic retinopathy and haplotypes of IL-1A and ILb carrying at least 3 copies of allele 2 of these genes as being associated with clinically-significant macular edema. Thereby, the scope of the claims does not bear a reasonable correlation to the scope of enablement provided by the specification and undue experimentation would be required to practice the full scope of the claims because this would require randomized searching of IL-1 genes and the entire genome for additional alleles which may be analyzed for their association with sight-threatening diabetic retinopathy. While it may be obvious to try to search for additional polymorphisms correlated with this disease and while it is within the skill of the art to detect sequence variations in general, it is highly unpredictable as to which other, if any, polymorphisms in unspecified known and unknown genes would be correlated with different forms of sight-threatening diabetic retinopathy. The methodology as defined in claim 9 in which polymorphisms are identified in IL-1A, ILb and IL-1RN genes, polymorphisms are identified in "other genes associated with sight-threatening diabetic retinopathy" and then a multiple genetic polymorphism pattern is developed and used to determine risk of sight-threatening diabetic retinopathy is considered to be a research project, rather than a methodology that allows one of skill in the art to determine a patient's risk of developing sight-threatening diabetic retinopathy without undue experimentation. The specification does not teach what number of polymorphisms must be carried by a patient in order to determine that the patient has an increased or decreased

risk of developing or having sight-threatening diabetic retinopathy. The specification does not exemplify or describe any particular "multiple genetic polymorphism patterns associated with risk of sight threatening diabetic retinopathy" and does not provide sufficient guidance as to how to identify such multiple patterns without extensive experimentation. Furthermore, the specification has established specific correlations between IL-1RN (VNTR) allele 2,2 patterns and proliferative diabetic retinopathy and IL-1A (-511) and ILb(-511) allele 2 patterns and clinically-significant macular edema, but has not established a general correlation between IL-1RN (VNTR) polymorphisms or IL-1A/ILb genotypes and other types of diabetic retinopathy. The specification has not provided any data regarding the occurrence of these IL-1RN and clinically-significant macular edema or the occurrence of IL-1A/ ILb genotypes and proliferative diabetic retinopathy and has not established that polymorphisms associated with clinically-significant macular edema are also associated with proliferative diabetic retinopathy and vice versa. Accordingly, in view of the lack of information provided in the specification as to how to reasonably identify other alleles without undue experimentation and in view of the unpredictability in the art in correlating the presence of an allele with a disease, particularly in correlating the presence of an IL-1 polymorphism with sight-threatening diabetic retinopathy, the specification has not adequately taught one of skill in the art how to practice the claimed invention as it is broadly claimed.

6. Claims 1-9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-9 are indefinite over the recitation of "genetic polymorphism pattern at IL-1A, ILb(-511), and IL-1RN" and "genetic polymorphism pattern for the genes IL-1A, ILb and "IL-1RN" because the claims do not set forth which particular polymorphisms are encompassed by the claims. Because the specification does not provide a clear definition for these terms and phrases and because each of the interleukin genes contains multiple polymorphisms, it is unclear as to whether the claims intend to refer to a specific polymorphism or to any polymorphism. For example, it is unclear as to whether "IL-1RN" refers to the IL-1RN (VNTR) polymorphism or the IL-1RN (+2018) polymorphism. Clarification of the claims is required.

Claim 3 is indefinite over the recitation of "whether the means for determining the genetic polymorphism pattern include restriction enzyme digestion" because the recited means constitute methods, rather than means. While it is clear as to what is meant by a kit containing reagents required for performing restriction enzyme digestion (i.e., wherein said means includes the restriction enzymes *NcoI, AvaI and Bsu36I*), it is unclear as to what is intended to be meant by a kit comprising "restriction enzyme digestion".

Claims 4-8 are indefinite over the recitation of "control patterns of known polymorphisms" because it is unclear as to what constitutes the control pattern. The claims do not clearly set forth the properties of the control pattern, such as whether the control pattern contains polymorphisms in the interleukin genes that are known to be associated with sight-threatening diabetic retinopathy, or contain any polymorphism in any interleukin gene or contain any polymorphism in any gene wherein the polymorphisms are associated with some unstated

disease or are just simply polymorphisms not particularly correlated with a disease. Because the properties of the control pattern are not set forth in the claims, it is unclear as to how performing the step of comparing the polymorphism pattern of the diabetic patient with any "control polymorphism pattern" results in the identification of diabetic patients at increased risk of having sight-threatening diabetic retinopathy.

Claims 7 and 8 are indefinite over the recitation of "the DNA genetic polymorphism pattern associated with increased risk of clinically-significant macular edema" because this phrase lacks proper antecedent basis. While the claims previously refer to sight-threatening diabetic retinopathy, the claims do not previously refer to clinically-significant macular edema. That is, the claims do not clearly set forth the relationship between sight-threatening diabetic retinopathy and clinically-significant macular edema. Furthermore, it is unclear as to whether this phrase refers to the fact that the diabetic patient has this polymorphism pattern or whether this phrase is intended to constitute a step of interpreting the data obtained by comparing polymorphism patterns. For example, it is unclear as to whether the claims are intended to be limited to a method wherein the presence of a polymorphism pattern comprising IL-1A 2,2 and ILb 1, 2 is indicative of an increased risk of developing clinically-significant macular edema. Similarly, claim 8 is indefinite over the recitation of "the DNA genetic polymorphism pattern associated with decreased risk of proliferative diabetic retinopathy" because this phrase lacks proper antecedent basis and it is unclear as to how this phrase is intended to further limit the claim. It is also unclear as to how claim 8 is intended to be further limiting from claim 7. For example, it is unclear as to whether

the diabetic patient has both the IL-1A/ILb and IL-1RN polymorphism patterns or whether diagnosis is based on the presence of both types or either type of polymorphism pattern.

Claims 7 and 8 are indefinite and confusing over the recitation of "presence at the combined loci of IL-1A plus ILb of at least three copies of the rarer allele for each loci (allele 2) between the two loci". The claims should be amended to clearly set forth a Markush group listing the possible combined IL-1A and ILb patterns, e.g. "wherein said polymorphism pattern is selected from the group consisting of (a) IL-1A (-889) 2,2 and ILb (-511) 2,2; (b) IL-1A (-889) 1, 2 and ILb (-511) 2, 2; and (c) IL-1A (-889) 2,2 and ILb (-511) 1,2.

Claim 9 is indefinite and vague over the recitation of "determining the number of polymorphisms" and "identifying diabetic patients expressing a multiple genetic polymorphism pattern" because the claim does not clearly state what constitutes a multiple genetic polymorphism pattern and this phrase is not defined in the specification and there is no statement in the claims as to what number of polymorphisms would be required to determine whether the patient was at risk of having sight-threatening diabetic retinopathy.

7.The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to

the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1 and 2 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mansfield (Gastroenterology (1994) 106:637-642) .

The claims are drawn to kits for identification of a patient's genetic polymorphism pattern. However, it is noted that in claims to products, such as kits, the intended use of the product does not carry weight with respect to the obviousness of the product.

Mansfield teaches methods for detecting polymorphisms at position -511 of the ILb gene and at position -889 of the IL-1A gene and for detecting VNTR alleles of IL-1 RN. In the method disclosed by Mansfield, PCR is performed using primers complementary to sequences flanking the -511 allele of ILb which consist of the same sequences as instant SEQ ID NO: 3 and 4, primers complementary to sequences flanking the -889 allele of IL-1A which consist of the sequences identical to instant SEQ ID NO: 9 and 10 and primers complementary to sequences flanking the VNTR allele of IL-1 RN which consist of sequences identical to instant SEQ ID NO: 5 and 6 (see Table 2). The method of Mansfield further requires the use of reagents for performing PCR including a means for collecting DNA, DNA amplification means and a DNA detection means. Accordingly, Mansfield teaches a method which requires the use of reagents for the primers of SEQ ID NO: 1, 2, 3, 4, 9 and 10, DNA collection means and DNA amplification means. Mansfield does not teach packaging these reagents into a kit. However, reagent kits for

performing DNA detection assays were conventional in the field of molecular biology at the time the invention was made and therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have packaged the primers and DNA collection means required to practice the method of Mansfield into a kit for the expected benefits of convenience and cost-effectiveness for practioners of methods for detecting IL-1 RN (VNTR), IL-1A (-889) and ILb (-511) polymorphisms. With respect to claim 1, the amplification reagents, such as polymerase, disclosed by Mansfield are considered to be a means for determining the genetic polymorphism pattern for IL-1A (-889), ILb (-511) and IL-1RN (VNTR) because the amplification reagents allow for the amplification of sequences containing the stated polymorphisms. Thereby, the kits suggested by Mansfield containing DNA sample collection means and amplification reagents meets the limitations of claim 1.

8. Claim 3 is rejected under 35 U.S.C. 103(a) as being unpatentable over Mansfield in view of Kornman (U.S. Patent 5,686,246).

Mansfield teaches methods for detecting polymorphisms at position -511 of ILb and at position -889 of IL-1A and for detecting VNTR alleles of IL-1 RN. In the method disclosed by Mansfield, PCR is performed using primers complementary to sequences flanking the -511 allele of ILb which consist of the same sequences as instant SEQ ID NO: 3 and 4, primers complementary to sequences flanking the -889 allele of IL-1A which consist of the same sequences as instant SEQ ID NO: 9 and 10 and primers complementary to sequences flanking the VNTR allele of IL-1 RN which consist of the same sequences as instant SEQ ID NO: 5 and 6

(see Table 2). The method of Mansfield also requires the use of reagents required to perform PCR including a means for collecting DNA, DNA amplification means and a DNA detection means. Mansfield (page 639) further teaches that the IL-1A (-889) polymorphism may be detected by restriction enzyme digestion with *NcoI* and the ILb (-511) polymorphism may be detected by restriction enzyme digestion with *AvaI*. Mansfield does not teach detecting the ILb (-511) polymorphism using the restriction enzyme *Bsu36I* and does not teach packaging the reagents required to detect the polymorphisms into a kit.

However, Kornman (col. 6) teaches that the ILb (-511) polymorphism may be detected using the restriction enzyme *Bsu36I* and specifically teaches that allele 2 of ILb (-511) contains a complete *Bsu36I* site. Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Mansfield so as to have also detected allele 2 of the ILb (-511) polymorphism by digestion with *Bsu36I* because Kornman teaches that this is an effective means for directly detecting the presence of Ilb (-511) allele 2. The resulting modified method of Mansfield thereby requires the use of reagents for collecting a DNA sample, the primers of SEQ ID NO: 1, 2, 3, 4, 9 and 10, and the restriction enzymes *NcoI, AvaI* and *Bsu36I*. In view of the conventionality of reagent kits for performing DNA detection, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have packaged the DNA collection means, restriction enzymes and primers required to practice the method of Mansfield into a kit for the expected benefits of convenience and cost-

effectiveness for practioners of methods for detecting IL-1 RN (VNTR), IL-1A (-889) and ILb (-511) polymorphisms.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is (703) 308-2199. The examiner can normally be reached on Monday-Thursday from 6:30 AM-5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached on (703)-308-1152. The fax number for the Technology Center is (703)-305-3014 or (703)-305-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to the receptionist whose telephone number is (703) 308-0196.

Carla Myers

October 4, 2000

Carla Myers
CARLA J. MYERS
PRIMARY EXAMINER